Adult idiopathic isolated ACTH deficiency: a short series and literature review

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Submitted: 2013-09-12 Accepted: 2013-10-28 Published online: 2013-12-03

Key words: **adult idiopathic isolated ACTH deficiency; clinical characteristics; diagnosis; and misdiagnosis**

Neuroendocrinol Lett 2013; **34**(7):693–700 **PMID:** 24463998 NEL340713A09

Abstract

OBJECTIVES: Adult idiopathic isolated ACTH deficiency (AIIAD) is an underestimated disorder which is frequently misdiagnosed. We presented 3 new Chinese AIIAD cases, summarized their clinical characteristics and analyzed the available literature.

METHODS: Three cases of AIIAD managed in Chinese PLA General Hospital during the period 1998–2003 were retrospectively identified. We have collected information on clinical presentation, laboratory findings and treatment response. The clinical characteristics were summarized and pertinent literatures were analyzed.

RESULTS: Our 3 cases with AIIAD aged 52–68 years old were misdiagnosed for a long period of time. Clinical features of AIIAD were summarized by reviewing the limited literature: 1. Most patients were over 40 years; 2. Clinical presentations were insidious; 3. Usually no pigmentation; 4. Hypogonadism and amenorrhea could present; 5. mild hypoglycemia, hyponatremia, normal-high potassium, mild anemia, lymphocytosis and eosinophilia could present; 6. With low or absent cortisol, normal secretion of pituitary hormones other than ACTH; 7. High prevalence of thyroid disorder; 8. Usually present concomitantly with other autoimmune disease, which usually disappeared on steroid replacement; 9. Absence of structural pituitary defects except for empty sella; 10. No evidence in any infiltration, trauma, surgery, infectious or radiotherapy, or glucocorticoid medication; 11. No growth abnormalities.

CONCLUSION: AIIAD is an unspecified and underestimated condition with much misdiagnosis. We summarized the clinical features to improve the recognition. Indeed, every patient with unexplained hyponatremia and malaise, particularly in patients with autoimmune diseases, needs to be evaluated for the possibility of AIIAD.

ORIGINAL ARTICLE

INTRODUCTION

Isolated deficiency of a single anterior pituitary hormone in the setting of no ascertainable disease of the pituitary gland or hypothalamus is frequently encountered in endocrine clinical practice. Most commonly patients present with either isolated gonadotrophin deficiency (King & Hayes 2012) or isolated growth hormone deficiency (Doga *et al.* 2006). On the other hand, idiopathic isolated ACTH deficiency (IIAD) is generally considered rare and limited published data related to this disorder exists.

IIAD can be congenital (congenital idiopathic isolated ACTH deficiency (CIIAD) or appear later in life (adult idiopathic isolated ACTH deficiency (AIIAD) (Andrioli *et al.* 2006).

AIIAD is characterized by secondary adrenal insufficiency (low ACTH with low or absent cortisol production) and normal secretion of pituitary hormones other than ACTH. Etiology cannot be readily explained by reasons such as abrupt cessation of exogenous glucocorticoid replacement or presence of structural pituitary defects (Andrioli *et al.* 2006). Few cases of AIIAD are reported in the world, less so in China with only 4 case reports in Chinese adults at the time of this publication (Gu 2006; Sun 2000; Zheng 1997; Long 2008). As the clinical presentation of AIIAD varies and lacks in specificity, we suspect that misdiagnosis of this condition is common. Thus, the prevalence of AIIAD is likely underestimated. Herein, we present 3 new Chinese AIIAD cases from the Chinese PLA general Hospital`s practice over the last 15 years. We provide a summary of the clinical characteristics of AIIAD both from our experience and the review of literature.

MATERIALS AND METHODS

Three cases of AIIAD managed in Chinese PLA General Hospital during the period 1998–2003 were retrospectively identified. We have collected information on clinical presentation, laboratory findings and treatment response. The clinical characteristics were summarized and pertinent literatures were analyzed.

RESULTS

Cases data

Case1. A 53-year-old man was referred to our department for evaluation and treatment of weakness, fatigue and unintentional weight loss. Initially, one year prior to admission the patient noted progressive weakness, anorexia with 10 kg weight loss, nausea, dizziness accompanied by hypotension, lower extremity myalgia and hair loss. He complained of erectile dysfunction and decreased libido. He denied history of headaches or visual field loss. In the local hospital, his blood glucose, hemoglobin and upper gastrointestinal endoscopy were normal. Thyroid function tests revealed increased TSH of 14.5 μIU/mL with normal levels of T_3 and T_4 with positive thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb). At that time, patient was diagnosed and treated for Hashimoto's thyroiditis without any significant symptomatic improvement. Past medical history was significant for a traumatic brain injury during a flight accident 27 years ago when during which he experienced a transient loss of consciousness and fractured one of the thoracic vertebras. He had never taken any form of glucocorticoid medication. He was an ex-smoker.

On admission to our hospital, patient's blood pressure (BP) was 80/45 mmHg, heart rate was 45/min, and body mass index (BMI) was 19.9 kg/m^2. Skin examination was significant for hypotrichosis and normal pigmentation. Thyroid gland was palpable with 1st degree and medium texture. The heart sounds were weak. Otherwise, physical exam was normal. Laboratory examination revealed low basal plasma ACTH, plasma cortisol, and 24 hour urinary free cortisol levels. Plasma ACTH was 3.9 pmol/L (normal range: 0–10.2 pmol/L) at 0 am and was 4.9 pmol/L (normal range: 5.1–18.9 pmol/L) at 8 am. Plasma cortisols at both 0am and 8am were lower than 31.3 nmol/L (normal range: 185.0–594.8 nmol/L). Urinary free cortisol in 24 hour (UFC) was less than 31.3 nmol (normal range: 55.2–345 nmol). ACTH and cortisol levels failed to adequately increase in response to insulin (0.1 u/kg) tolerance test (ITT). ACTH secretion peak was 8.2 pmol/L and cortisol peak was less than 31.3 nmol/L. ACTH stimulation test (ACTH 25 u intravenously for 3 days) indicated normal adrenal response at the 2nd day with UFC of 135.7 nmol and 3rd day with UFC of 348.5 nmol. Other work up revealed TSH of 14.5 μIU/mL and FT_4 of 25.3 pmol/L; FSH 8.4 IU/L, LH 10.7 mIU/L, T 22.2 nmol/L, growth hormone (GH) 1.1 ng/mL. GH peak was 22 ng/mL stimulated by ITT, LH peak was 47.8 mIU/L by GnRH stimulation test and TSH and PRL secretion by TRH stimulation test was demonstrated to be intact with TSH peak of 38.2 μIU/mL. Serum sodium was 131 mmol/L, potassium was 4.3 mmol/L and fasting blood glucose was 4.7 mmol/L. Adrenal glands appeared to be normal on CT imaging and pituitary MRI revealed empty sella. Electrocardiography showed sinus bradycardia. Patient was diagnosed with adult idiopathic isolated ACTH deficiency and was initiated on prednisone acetate 5 mg/d leading to dramatic clinical improvement.

Case 2. A 48-year-old woman was admitted to our hospital because of fatigue and dizziness for over period of 4 years. She also complained of palpitations, increased perspiration, anorexia without weight loss, abdominal distension, constipation, weakness, lower extremity pain and numbness. Blood pressure was 80–90/50–60 mmHg. Two years prior to admission, she noted oligomenorrhea and menstrual irregularities when she was diagnosed with menopause. She denied history of glucocorticoid medication use. On admission, blood pressure was 108/62 mmHg (lying) and 80/45 mmHg

(sitting), heart rate was 78/min and BMI 25 kg/m^2. No hyperpigmentation was noted. Lung, heart and abdomen examination were negative. Pathological reflexes could not be induced. Laboratory tests revealed 24 hour UFC less than 25.7 nmol, cortisol levels lower than 25.7 nmol/L and ACTH levels below 2.2 pmol/L at 0 am, 8 am and 4 pm, respectively. TSH, FT_3, FT_4, TGAb, TPOAb, LH, FSH, PRL, estrogen and growth hormone were found to be normal both at baseline and after stimulation. Biochemical evaluation indicated normal electrolytes and blood glucose. ESR was 2 mm/h. IgG, IgM and serum protein electrophoresis analysis were normal. Pituitary MRI was negative. Adult idiopathic isolated ACTH deficiency was diagnosed and prednisone acetate 5 mg/d was administered. Patient`s fatigue and dizziness resolved soon after treatment initiation and her menses normalized.

Case 3. A sixty-three years old man was hospitalized with complaints of general weakness, fatigue, weight loss of 12 kg, nausea and lack of appetite for about seven months. His serum sodium on admission was 110 mmol/L and increased to 128 mmol/L with appropriate therapy. Upper gastrointestinal endoscopy showed superficial gastritis and he was treated accordingly, but the symptoms did not resolve and he progressed to develop severe diarrhea and abdominal distension. This symptomatology prompted presentation to the emergency room where patient`s cortisol levels were recorded as low (no documentation) and he was administered hydrocortisone 100 mg/day for 3 days, followed by prednisone acetate 5 mg/day. Immediately after glucocorticoid therapy initiation, the clinical symptoms and signs dramatically improved. Otherwise, past medical history included allergic rhinitis, intermittent skin itching and rash in the lower extremities for one year.

Prior to presentation to our hospital, prednisone acetate was stopped for at least for 5 days. On admission, his temperature was 36.4 °C, heart rate 66/min, BP 120/70mmHg, BMI 18.2 kg/m^2. The skin was pale without hyperpigmentation. No changes in genital and armpit hair were noted. Scattered erythematous rash was found in the lower extremity. Thyroid exam revealed a 1st degree enlargement and soft consistency. Physical exam was otherwise normal. Laboratory investigations were significant for serum cortisol levels of below 25.7 nmol/L at 0 am, 8 am and 4 pm and ACTH levels of lower than 2.2 pmol/L at each time points. UFC from 24 hour collection was 26.8 nmol. TT_4 was 170.5 nmol/L, TT_3 was 1.36 nmol/L, FT_3 4.15 pmol/L, FT_4 23.62 pmol/L, TSH 2.45 mU/L,TGAb 197.8 IU/mL, TPOAb 444.7 IU/mL, T 24.5 nmol/L, E_2 102.28 pmol/L, LH 10.3 mIU/L, PRL 33.19μg/L, FSH 29.84 IU/L and P 1.67 nmol/L. GH 0.6 ng/mL, WBC 7.31×10^9/L, L 66.5%, Hb120 g/L. Serum K was 3.2 mmol/L and Na 144 mmol/L. ESR, TB antibodies and autoimmune antibodies were normal. CT imaging of adrenal glands and MRI of pituitary gland were normal. Based on these results, the patient was diagnosed as adult idiopathic isolated ACTH deficiency. After the administration of prednisolone acetate 5mg in the morning and 2.5 mg in the afternoon, the patient felt much better and his fatigue, nausea and electrolyte abnormalities resolved. Interestingly, the allergic rhinitis, skin itching and rash disappeared or improved with prednisone acetate treatment.

Summary of the pertinent clinical characteristics of the 3 AIIAD patients

Clinical characteristics of the 3 cases with AIIAD were summarized in Table 1. They aged 52–68 years old. Clinical presentations were unspecific and were misdiagnosed for a long period of time. Hyponatremia appeared in 2 of the cases. TpoAb was positive in 2 cases. Commitment disease includes Hashimoto's thyroiditis in in one case and allergic rhinitis, skin itching and rash in another case, which disappeared on steroid replacement therapy. One patient was revealed empty sella by MRI imaging and no evidence of pituitary infiltration, trauma, surgery, infection and radiotherapy, glucocorticoid medication.

Clinical categories of isolated adrenal deficiency by summarizing available literature

By reviewing literatures, different categories of isolated adrenal deficiency (IAD) were summarized in Table 2, from which we can found IAD can be firstly classified into acquired or idiopathic IAD (IIAD) categories. Adult IIAD (AIIAD) was one subtype of IIAD.

DISCUSSION

Idiopathic isolated ACTH deficiency (IIAD) is a rare disorder, first reported by Steinberg in 1954 (Steinberg *et al.* 1954). Adrenal insufficiency cases could be caused either by pathology at the level of the adrenal gland (primary hypoadrenalism) or at the level of hypothalamus or pituitary gland (secondary hypoadrenalism) (Kuhn & Goudouet-Getti 2008). Secondary hypoadrenalism is commonly associated with other anterior pituitary hormone deficiencies or, rarely, can be isolated. The most common causes of isolated secondary hypoadrenalism include abrupt decrease of chronic exogenous or endogenous glucocorticoids. The latter frequently occurs following the removal of an ACTH producing tumour in Cushing's syndrome, which is usually manifested as isolated ACTH deficiency. Pituitary and hypothalamic lesions, including tumors, infections, autoimmune lesions, granulomatous infiltration, lymphocytic infiltration and trauma, can also cause secondary hypoadrenalism and usually present with multiple pituitary hormone deficiencies. Idiopathic isolated ACTH deficiency is a rare cause of secondary adrenocortical insufficiency as well as of isolated ACTH deficiency, and could present as congenital as well as maturity onset types (AIIAD) (Andrioli *et al.* 2006).

Tab. 1. Clinical characteristics of the 3 cases with AIIAD.

	Case 1	Case 2	Case 3	Normal range for lab
Sex	M	F	M	–
Age at onset, yr.	52	44	62	–
Age at diagnosis, yr.	53	48	63	–
Diagnosis delay, yr.	1	4	0.58	–
Initial symptoms	weakness, fatigue and unintentional weight loss	fatigue, dizziness, palpitations, increased perspiration, anorexia	general weakness, fatigue, weight loss and nausea	–
hypogonadism	erectile dysfunction and decreased libido	oligomenorrhea and menstrual irregularities		–
Weight change,	10 kg/yr.	0	12 kg/0.58 yr.	–
Diagnosis before	Hashimoto's thyroiditis	menopause	superficial gastritis	–
Commitment disease	Hashimoto's thyroiditis	-	allergic rhinitis, skin itching and rash	–
BP, mmHg	80/45	108/62	120/70	–
ACTH 8am, pmol/L	4.9	<2.2	<2.2	5.1–18.9
Cortisol 8am, nmol/L	<31.25	<25.7	<25.7	185.0–594.8
UFC, nmol	<31.25 twice	<25.7	26.8	55.2–345
GH, ng/ml	1.1	1.6	0.6	0.06–5.0
LH, mIU/L	10.7	7.4	10.3	
FSH, IU/L	8.4	12.1	29.84	
T, nmol/L	22.2	250*	24.5	T, 8.4–28.7; E_2, 69.4–905.4 and 70.0–1938.0 pmol/L
Prolactin, µg/L	22.3	21.1	33.19	2.1–17.7 for male; 2.8–29.2 for female
TSH, mIU/L	14.5 and 6.9	1.7	2.45	0.35–5.5
FT4, pmol/L	25.3 and 16.3	25.4	23.62	10.4–24.3
TpoAb, IU/ml	398.6	39.8	444.7	<30%
TGAb, IU/ml	223.5	42.3	197.8	<30%
Na, mmol/L	131	138	110	135–155
K, mmol/L	4.3	4.0	3.2	3.5–5.5
Therapy	prednisone acetate 5 mg/d	prednisone acetate 5 mg/d	prednisone acetate 5 mg/d	–
Response to glucocorticoid	dramatic clinical improvement	fatigue and dizziness resolved soon after treatment initiation and her menses normalized	clinical symptoms and signs dramatically improved; allergic rhinitis, skin itching and rash disappeared or improved	–
Pituitary MRI	empty sella	normal	normal	

*E_2; Abbreviations used: AIIAD, Adult idiopathic isolated ACTH deficiency; ACTH, corticotropin; BP, Blood pressure; BMI, body mass index; E_2, estradiol; F, female; FT4, free thyroxine; FSH, follicle-stimulating hormone; GH, growth hormone; K, potassium; LH, luteinizing hormone; M, male; MRI, Magnetic resonance imaging; Na, natrium; T, testosterone; TpoAb, thyroid Peroxidase Antibodies; TGAb, thyroglobulin Antibodies; TSH, thyroid-stimulating hormone; UFC, 24-hour urinary free cortisol; WBC, White Blood Cell.

The prevalence of idiopathic isolated ACTH deficiency (IIAD) remains to be determined. IIAD accounts for only a small part of secondary AI and the rarity of its occurrence explains the uncertainties in its epidemiology and etiology. Recently, the largest collection of DNA sample analysis from multiple centers in European and northern American populations demonstrated 91 congenital IAD patients altogether up to 2012 (Couture *et al.* 2012). Another report (Osuwannaratana *et al.* 2008) describing the etiology of adrenal insufficiency

Tab. 2. Different categories of isolated adrenal deficiency (IAD).

	Acquired IAD	Idiopathic IAD (IIAD)		
		Congenital IIAD (CIIAD)		Adult IIAD (AIIAD)
		Neonatal onset	Late onset	
Age onset, yr.	any age	new born	9±6.7(2–29yr.)	>40
Familial or sporadic	sporadic	familial	familial	sporadic
Common chief complaints	fatigue, weakness, anorexia, weight loss	neonatal hypoglycemia; seizures; prolonged cholestatic jaundice	growth retardation, fatigue, anorexia, weight loss	fatigue, weakness, anorexia, weight loss
Pathogenesis	abrupt cessation of exogenous glucocorticoid replacement; removal of ACTH-producing adenoma, *et al.*	TPIT gene mutation account for 65% of neonatal-onset complete IAD	unclear	unclear; close related to autoimmunity
Treatment	hydrocortisone or prednisone	hydrocortisone	hydrocortisone before epiphyseal closure and prednisone after epiphyseal closure	hydrocortisone or prednisone

in 73 Thai Children showed that 9.1% of secondary adrenal insufficiency patients had isolated ACTH deficiency and only 1.4% had IIAD. Hannon MJ. (Hannon & O'Halloran 2011) revealed that truly validated cases of AIIAD where there was no evidence of pituitary inflammation, infiltration and trauma and no cause could be found were very rare and no large series had been reported and the largest series revealed just 103 cases in total at that time. In 2005, estimated prevalence of adult IAD in Japan was 7.3 per 100,000 (an average over 10-year period) in Tokunoshima and 3.8 per 100,000 in the Chuetsu district (Yamamoto & Kamoi 2008). In China, only 4 case reports of adult IIAD and no congenital IIAD cases were reported. Since we have the largest population in the world, the prevalence of this disease in China could be underestimated.

It is likely that congenital IIAD has genetic origin (Hannon & O'Halloran 2011). The etiology of adult IIAD remains uncertain, however autoimmunity might play a role in adult IIAD. Studies supporting the autoimmune etiology for AIIAD were attempted. Antibodies against a 22 k Dalton pituitary protein have been detected in patients with IIAD and lymphocytic hypophysitis (Takao *et al.* 2001; Kikuchi *et al.* 2000); Co-existing autoimmune disease was found in 63% of patients with secondary adrenal insufficiency of unknown etiology (Kasperlik-Zaluska *et al.* 2003); Association of IIAD with type 1 diabetes (Giustina *et al.* 1988) , polyglandular autoimmune failure, vitiligo, pernicious anaemia, idiopathic thrombocytopenic purpura (Jujo *et al.* 2007), alopecia universalis (Sheehan & Islam 2009),ulcerative colitis (Sheehan & Islam 2009), Crohn's disease (Kalambokis *et al.* 2004), focal segmental glomerulosclerosis (Yamada *et al.* 2010) and late onset of hypogonadism (Sato *et al.* 2008) were reported. IIAD is also frequently associated with autoimmune thyroid disease, including Hashimoto`s thyroiditis (Jujo *et al.* 2007; Okuno *et al.* 1993), primary hypothyroidism (Hannon & O'Halloran 2011; Miller & Horst 1982; Yamamoto *et al.* 1976), Graves` disease (Miyauchi *et al.* 2004) and silent thyroiditis (Sheehan & Islam 2009). It was reported that thyroid autoantibodies were positive in 60% of patients with secondary adrenal failure (Kasperlik-Zaluska *et al.* 2003). Furthermore, autoimmune diseases were completely or partially relieved after the replacement of glucocorticoid agents. In more than 70% of patients with autoimmune thyroid disorder the abnormality was reversed by glucocorticoid replacement (Murakami *et al.* 1993). In our report, among the 3 cases, 2 patients presented with elevated TSH,TPO and TG antibodies and one with allergic rhinitis, skin itching and rash, which disappeared after prednisolone acetate treatment.

Traumatic brain injury has been described as a cause of isolated pituitary hormone deficiencies including AIIAD (Andrioli *et al.* 2006). A patient with post-traumatic isolated ACTH deficiency was reported to spontaneously recover 9 months after the event (Karavitaki *et al.* 2006). Our first patient had a brain trauma 27 years ago and we had no way to confirm what the relationship between the brain trauma and pituitary ACTH deficiency, but empty sella was found in this patient. Our report is consistent with other reports (Gulcan *et al.* 2007) indicating that empty sella might be related to the pathogenesis of isolated ACTH deficiency. It was reported that, of the nine patients with secondary adrenal insufficiency and autoimmune disease, six had a partially or fully empty sella revealed by pituitary MRI and showed positive antibodies against corticotroph or mammotroph cells (Kasperlik-Zaluska *et al.* 1998; Komatsu *et al.* 1988). The relationship of brain trauma, autoimmune pituitary destruction and empty

sella is yet to be fully characterized. We hypothesize that very tiny injuries of pituitary corticotrophin cells and protein exposure induced by brain trauma trigger an autoimmunity process with the generation of autoimmune antibody. As a result, pituitary corticotrophin cells are destroyed possibly leading to empty sella. This can explain why only loss of ACTH secretion and none of other pituitary hormones occur in trauma and empty sella. However, more evidence is needed to support this hypothesis.

Several candidate genes including proopiomelanocortin (POMC) gene, transcription factors of NeuroD (Poulin *et al.* 1997), Dtpx1 (Lamonerie *et al.* 1996), Tpit (Couture *et al.* 2012) and Ikaros (Ezzat *et al.* 2005) were investigated in IIAD. The loss-of-function mutations in the TPIT gene were detected in a neonatal onset form of congenital isolated ACTH deficiency (IAD) (Pulichino *et al.* 2004). TPIT mutations were responsible for 60–65% of patients with neonatal-onset complete IAD while no mutation was found in partial or late onset IAD (Couture *et al.* 2012; Vallette-Kasic *et al.* 2005). A total of 12 different loss-of-function TPIT mutations have been identified (Vallette-Kasic *et al.* 2007). So far, gene mutations have not been found to play any role in the pathogenesis of AIIAD (Couture *et al.* 2012; Pham *et al.* 2011).

Clinical manifestations of AIIAD are similar to those found in primary AI although usually less severe. If unrecognized, the patients usually fell relatively well until intervening events trigger an acute adrenal crisis. It is characterized by extreme fatigue, fever, acute abdominal pain, nausea and vomiting, diarrhea, severe hypotension and hypoglycemia, and may be life threatening without prompt theapy. Indeed, its clinical presentation can be very unspecific and variable (Hannon & O'Halloran 2011; Stacpoole *et al.* 1982), such as asthenia, anorexia, weakness, nausea, abdominal pain, unintentional weight loss and tendency to hypoglycemia, making it a difficult diagnostic challenge. We summarized the clinical features of AIIAD based on our cases and literature review as follows: 1. most patients had an age of over 40 years old at the time of symptom onset (Burke *et al.* 1979; Odell 1966); 2. Clinical presentation is insidious, and usually includes fatigue, malaise, weakness, nausea and weight loss, over a long period of time; 3. Patients present without hyperpigmentation (which is common in primary adrenal insufficiency); 4. Symptoms of hypogonadism in men and amenorrhea in women could be present, but no significant abnormality in gonadal axis is usually found. So, this abnormality could be functional; 5. Blood chemistries may reveal mild hypoglycemia, hyponatremia and normal-high potassium levels. Unlike primary AI, secondary AI is not associated with lack of aldosterone, thus symptoms and signs of mineralocorticoid deficiency (salt-craving, postural hypotension, electrolyte abnormalities) are usually absent (Salvatori 2005; Parenti *et al.* 2007). Hyponatremia has been reported in 88% of patients with primary adrenal insufficiency and 28% of IAD patients (Vasikaran *et al.* 1994). Two of the 3 IAD patients in our series presented with hyponatremia; 6. Patients might have mild anemia, lymphocytosis and eosinophilia. The presence of eosinophilia aids the diagnosis of acquired IIAD; 7. Low or absent cortisol production, low/low normal ACTH and normal secretion of pituitary hormones other than ACTH; 8. High prevalence of thyroid disorder (Murakami *et al.* 1993). A Polish study with idiopathic secondary adrenal failure found that thyroid autoantibodies were positive in 60% of patients (Kasperlik-Zaluska *et al.* 2003). Hannon MJ reported that half of the cases of acquired IIAD had a high plasma level of TSH (Hannon & O'Halloran 2011). 9. Associated diseases including idiopathic thrombocytopenic purpura, alopecia universalis, ulcerative colitis, Crohn's disease, focal segmental glomerulosclerosis, late onset hypogonadism are common; 10. The concomitant autoimmune disorders, though not typical of AI, seem to be closely related to the hypoadrenal condition because they disappear on steroid replacement therapy; 11. Absence of structural pituitary defects except for empty sella; 12. No evidence of pituitary infiltration, trauma, surgery, infection and radiotherapy, glucocorticoid medication use or any other causes of pituitary dysfunction was identified; and 13. No growth abnormalities present.

The diagnosis can be made based on the clinical features above. Indeed, every patient with unexplained hyponatremia, malaise and weight loss needs to be evaluated for the possibility of AIIAD. The key step in the diagnosis is the laboratorial evaluation of pituitary-adrenal axis. Morning serum cortisol is usually the first step in the diagnostic work-up. Morning serum cortisol below 3 ug/dl is virtually diagnostic for adrenal insufficiency, or it can be excluded in the upper half of the normal range (Arlt & Allolio 2003; Salvatori 2005), whereas cortisol values comprised between 5–18 μg/dL require additional investigations. In secondary adrenal insufficiency (low baseline ACTH), insulin tolerance test (ITT) (regular insulin 0.1 U/kg as iv bolus in normal weight and 0.15 U/kg in overweight subjects, with measurement of blood glucose and cortisol at 0, 30 and 60 min) is considered the gold standard, but the glucagon stimulation test provides a viable alternative if insulin tolerance testing is contraindicated (Reimondo *et al.* 2008). Plasma ACTH concentration and prolonged ACTH infusion test are useful in differential diagnosis between primary and secondary adrenal insufficiency (Andrioli *et al.* 2006). But for some newly developed secondary hypoadrenalism, such as those who have recently undergone pituitary surgery or had a pituitary infarction, ACTH stimulation test might generate false-negative results (Salvatori 2005). Once the diagnosis of secondary AI has been established, normal concentrations of the other pituitary hormones, as well as the absence of structural pituitary defects, except for the typical changes in case of hypophysitis, have to

be ascertained. GnRH and TRH tests can be used to exclude the defects of other pituitary hormones while MR of the hypotalamic-pituitary region is necessary. Genetic testing has so far proven to be of little use in adult IIAD.

Treatment of AIIAD includes glucocorticoid replacement without need for other hormonal supplementation. It is important to keep in mind that thyroid supplementation should be administered after glucocorticoid substitution when the patient was complicated with primary hypothyroidism. Additionally, unlike primary AI, administration of mineralocorticoids is generally not necessary for AIIAD. Based on the present knowledge on cortisol production rate (Esteban *et al.* 1991), the recommended glucocorticoid replacement dose for patients with AI is lower than in the past, and in particular for patients with secondary AI (Salvatori 2005). For some patients with mild, near-to-asymptomatic disease, glucocorticoid replacement therapy may not be required except during stressful events; for symptomatic patients, replacement doses i.e., mean daily dose 20 mg (0.30 mg/kg) hydrocortisone or 25 mg (0.35 mg/kg) cortisone acetate, are usually sufficient , with two-thirds of the dose administered in the morning. Recent studies indicate that thrice-daily regimen more closely mimics the physiological steroid circadian profile (Howlett 1997; Mah *et al.* 2004). Long-acting glucocorticoids can also be used in equivalent doses (1 mg hydrocortisone = 1.25 mg cortisone acetate = 0.2 mg prednisolone = 0.03 mg dexamethasone) but this may result in unfavorably high nocturnal cortisol levels. ACTH replacement might be more physiologic than glucocorticoid replacement, but is not feasible. Monitoring of glucocorticoid replacement therapy essentially relies on clinical judgment as no laboratory parameter is fully reliable. Indeed, glucocorticoids need to be prescribed judiciously, using the lowest dose that improves the patient's symptoms as well as avoids side effects of over-replacement. Management of acute adrenal crisis requires immediate intravenous administration of 100 mg hydrocortisone, followed by 100–200 mg over the next 24 h and large volumes of saline under continuous cardiac monitoring (Andrioli *et al.* 2006). In general, patients with intact adrenal function secrete between 75 and 150 mg/d in response to major surgery (Salem *et al.* 1994). Thus 50mg of hydrocortisone every 8 hours is likely sufficient (Salvatori 2005).

In summary, adult IIAD is an underestimated condition with unspecific clinical presentation resulting in diagnostic challenge and frequent misdiagnosis. We summarized the clinical features based on our case analysis and literature review with the purpose to improve the recognition and decrease the rate of misdiagnosis. Indeed, every patient with unexplained hyponatremia, malaise and weight loss, particularly in patients with a history of autoimmune diseases or thyroid autoimmune disorder, needs to be evaluated for the possibility of AIIAD.

ACKNOWLEDGMENTS

The authors greatly appreciate Prof. Irina Bancos of Mayo Clinic for manuscript review and advice. The work has been partially supported by the National Natural Science Foundation of China (Project Grant No: 81270866). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1 Andrioli M, Pecori Giraldi F, Cavagnini F (2006). Isolated corticotrophin deficiency. Pituitary **9**: 289–295.
2 Arlt W, Allolio B (2003). Adrenal insufficiency. Lancet **361**: 1881–1893.
3 Burke CW, Moore RA, Rees LH, Bottazzo GF, Mashiter K, Bitensky L (1979). Isolated ACTH deficiency and TSH deficiency in the adult. Journal of the Royal Society of Medicine **72**: 328–335.
4 Couture C, Saveanu A, Barlier A, Carel JC, Fassnacht M, Fluck CE, Houang M, Maes M, *et al.* (2012). Phenotypic homogeneity and genotypic variability in a large series of congenital isolated ACTH-deficiency patients with TPIT gene mutations. The Journal of clinical endocrinology and metabolism **97**: E486–495.
5 Doga M, Bonadonna S, Gola M, Mazziotti G, Giustina A (2006). Growth hormone deficiency in the adult. Pituitary **9**: 305–311.
6 Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC, Loriaux DL (1991). Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. The Journal of clinical endocrinology and metabolism **72**: 39–45.
7 Ezzat S, Mader R, Yu S, Ning T, Poussier P, Asa SL (2005). Ikaros integrates endocrine and immune system development. The Journal of clinical investigation **115**: 1021–1029.
8 Giustina A, Candrina R, Cimino A, Romanelli G (1988). Development of isolated ACTH deficiency in a man with type I diabetes mellitus. Journal of endocrinological investigation **11**: 375–377.
9 Gu My PY, Yao Ll, Sheng Zy (2006). One case of isolated ACTH deficiency and literature review. Chinese Journal of Endocrinology and Metabolism **22**: 494–495.
10 Gulcan E, Gulcan A, Taser F, Korkmaz U, Erbilen E (2007). May primary empty sella turcica be a cause of isolated ACTH deficiency? A case report and the review of related literature. Neuro endocrinology letters **28**: 745–748.
11 Hannon MJ, O'halloran DJ (2011). Isolated acquired ACTH deficiency and primary hypothyroidism: a short series and review. Pituitary **14**: 358–361.
12 Howlett TA (1997). An assessment of optimal hydrocortisone replacement therapy. Clinical endocrinology **46**: 263–268.
13 Jujo T, Tomizuka T, Fuse M, Takizawa H (2007). [Isolated ACTH deficiency with Hashimoto's thyroiditis and idiopathic thrombocytopenic purpura]. Nihon Naika Gakkai zasshi The Journal of the Japanese Society of Internal Medicine **96**: 991–993.
14 Kalambokis G, Vassiliou V, Vergos T, Christou L, Tsatsoulis A, Tsianos EV (2004). Isolated ACTH deficiency associated with Crohn's disease. Journal of endocrinological investigation **27**: 961–964.
15 Karavitaki N, Wass J, Henderson Slater JD, Wade D (2006). A case of post-traumatic isolated ACTH deficiency with spontaneous recovery 9 months after the event. Journal of neurology, neurosurgery, and psychiatry **77**: 276–277.
16 Kasperlik-Zaluska AA, Czarnocka B, Czech W (2003). Autoimmunity as the most frequent cause of idiopathic secondary adrenal insufficiency: report of 111 cases. Autoimmunity **36**: 155–159.
17 Kasperlik-Zaluska AA, Czarnocka B, Czech W, Walecki J, Makowska AM, Brzezinski J, Aniszewski J (1998). Secondary adrenal insufficiency associated with autoimmune disorders: a report of twenty-five cases. Clinical endocrinology **49**: 779–783.
18 Kikuchi T, Yabe S, Kanda T, Kobayashi I (2000). Antipituitary antibodies as pathogenetic factors in patients with pituitary disorders. Endocrine journal **47**: 407–416.

19 King TF, Hayes FJ (2012). Long-term outcome of idiopathic hypogonadotropic hypogonadism. Current opinion in endocrinology, diabetes, and obesity **19**: 204–210.
20 Komatsu M, Kondo T, Yamauchi K, Yokokawa N, Ichikawa K, Ishihara M, Aizawa T, Yamada T, *et al.* (1988). Antipituitary antibodies in patients with the primary empty sella syndrome. The Journal of clinical endocrinology and metabolism **67**: 633–638.
21 Kuhn JM, Goudouet-Getti B (2008). [Primary and secondary adrenal insufficiency in adults]. La Revue du praticien **58**: 949–956.
22 Lamonerie T, Tremblay JJ, Lanctot C, Therrien M, Gauthier Y, Drouin J (1996). Ptx1, a bicoid-related homeo box transcription factor involved in transcription of the pro-opiomelanocortin gene. Genes & development **10**: 1284–1295.
23 Long J ZS (2008). Case report of isolated ACTH deficiency and literature review. Journal of Endocrine Surgery **4**: 235.
24 Mah PM, Jenkins RC, Rostami-Hodjegan A, Newell-Price J, Doane A, Ibbotson V, Tucker GT, Ross RJ (2004). Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. Clinical endocrinology **61**: 367–375.
25 Miller MJ, Horst TV (1982). Isolated ACTH deficiency and primary hypothyroidism. Acta endocrinologica **99**: 573–576.
26 Miyauchi S, Yamashita Y, Matsuura B, Onji M (2004). Isolated ACTH deficiency with Graves' disease: a case report. Endocrine journal **51**: 115–119.
27 Murakami T, Wada S, Katayama Y, Nemoto Y, Kugai N, Nagata N (1993). Thyroid dysfunction in isolated adrenocorticotropic hormone (ACTH) deficiency: case report and literature review. Endocrine journal **40**: 473–478.
28 Odell WD (1966). Isolated deficiencies of anterior pituitary hormones. Symptoms and diagnosis. JAMA : the journal of the American Medical Association **197**: 1006–1016.
29 Okuno S, Inaba M, Nishizawa Y, Morii H (1993). [Isolated ACTH deficiency associated with Hashimoto disease]. Nihon rinsho Japanese journal of clinical medicine **51**: 2721–2725.
30 Osuwannaratana P, Nimkarn S, Santiprabhob J, Likitmaskul S, Sawathiparnich P (2008). The etiologies of adrenal insufficiency in 73 Thai children: 20 years experience. Journal of the Medical Association of Thailand = Chotmaihet thangphaet **91**: 1544–1550.
31 Parenti G, Ricca V, Zogheri A, Serio M, Mannelli M, Peri A (2007). A case of hyponatremia caused by central hypocortisolism. Nature clinical practice Endocrinology & metabolism **3**: 369–375.
32 Pham LL, Garot C, Brue T, Brauner R (2011). Clinical, biological and genetic analysis of 8 cases of congenital isolated adrenocorticotrophic hormone (ACTH) deficiency. PloS one **6**: e26516.
33 Poulin G, Turgeon B, Drouin J (1997). NeuroD1/beta2 contributes to cell-specific transcription of the proopiomelanocortin gene. Molecular and cellular biology **17**: 6673–6682.
34 Pulichino AM, Vallette-Kasic S, Couture C, Brue T, Drouin J (2004). [Tpit mutations reveal a new model of pituitary differentiation and account for isolated ACTH deficiency]. Medecine sciences : M/S **20**: 1009–1013.
35 Reimondo G, Bovio S, Allasino B, Terzolo M, Angeli A (2008). Secondary hypoadrenalism. Pituitary **11**: 147–154.
36 Salem M, Tainsh RE, Jr., Bromberg J, Loriaux DL, Chernow B (1994). Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Annals of surgery **219**: 416–425.
37 Salvatori R (2005). Adrenal insufficiency. JAMA : the journal of the American Medical Association **294**: 2481–2488.
38 Sato Y, Tanda H, Kato S, Ohnishi S, Nakajima H, Nitta T, Akagashi K, Hanzawa T (2008). [Isolated ACTH deficiency in a late onset case of hypogonadism (LOH) not diagnosed by examination in an internal medicine clinic]. Hinyokika kiyo Acta urologica Japonica **54**: 573–575.
39 Sheehan MT, Islam R (2009). Silent thyroiditis, isolated corticotropin deficiency, and alopecia universalis in a patient with ulcerative colitis and elevated levels of plasma factor VIII: an unusual case of autoimmune polyglandular syndrome type 3. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists **15**: 138–142.
40 Stacpoole PW, Interlandi JW, Nicholson WE, Rabin D (1982). Isolated ACTH deficiency: a heterogeneous disorder. Critical review and report of four new cases. Medicine **61**: 13–24.
41 Steinberg A, Shechter FR, Segal HI (1954). True pituitary Addison's disease, a pituitary unitropic deficiency; fifteen-year follow-up. The Journal of clinical endocrinology and metabolism **14**: 1519–1529.
42 Sun Mz XL (2000). One case report to isolated ACTH deficiency with silent thyroiditis. Foreign Medical SciencesSection of Endocrinology **1**: 107.
43 Takao T, Nanamiya W, Matsumoto R, Asaba K, Okabayashi T, Hashimoto K (2001). Antipituitary antibodies in patients with lymphocytic hypophysitis. Hormone research **55**: 288–292.
44 Vallette-Kasic S, Brue T, Pulichino AM, Gueydan M, Barlier A, David M, Nicolino M, Malpuech G, *et al.* (2005). Congenital isolated adrenocorticotropin deficiency: an underestimated cause of neonatal death, explained by TPIT gene mutations. The Journal of clinical endocrinology and metabolism **90**: 1323–1331.
45 Vallette-Kasic S, Couture C, Balsalobre A, Gauthier Y, Metherell L, Dattani M, Drouin J (2007). The TPIT gene mutation M86R associated with isolated adrenocorticotropin deficiency interferes with protein: protein interactions. The Journal of clinical endocrinology and metabolism **92**: 3991–3999.
46 Vasikaran SD, Tallis GA, Braund WJ (1994). Secondary hypoadrenalism presenting with hypercalcaemia. Clinical endocrinology **41**: 261–264.
47 Yamada S, Bandai S, Masutani K, Tsuchimoto A, Noguchi H, Munakata M, Tsuruya K, Iida M (2010). Focal segmental glomerulosclerosis in a patient with isolated ACTH deficiency and reversible hypothyroidism. Clinical and experimental nephrology **14**: 168–172.
48 Yamamoto T, Kamoi K (2008). Prevalence of maturity-onset isolated ACTH deficiency (IAD) in 2005: Japanese cohort studies. Endocrine journal **55**: 939–941.
49 Yamamoto T, Ogihara T, Miyai K, Kumahara Y, Hirata Y (1976). Coexistent primary hypothyroidism and isolated ACTH deficiency. Acta endocrinologica **82**: 467–474.
50 Zheng Jj LY (1997). Case report of isolated ACTH deficiency. Chinese Journal of Endocrinology and Metabolism **3**: 161.